UNIKLINIK RWTH AACHEN
Klinik für Kinder- und Jugendmedizin
Sektion Neuropädiatrie und Sozialpädiatrie

RWTH AACHEN UNIVERSITY

Infections of the neonatal brain

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05.04.2016

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- Basic principles

- Clinical manifestations
- Diagnostic challenges
- Treatment

- Congenital infections
- Neonatal infections

Basic principles

- The physiological neonatal „immunodeficiency“
- Age at infection and lesion pattern
- Congenital infections - chronic infections
- Pathomechanisms of brain lesions

The physiological neonatal immunodeficiency

- Intrauterine

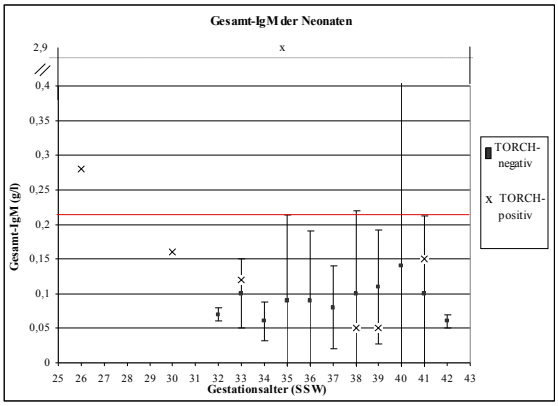
- All immunological subsystems?

- The preterm infant
- antibodies
- neutrophils

- The term born infant
- Antibodies - wrong tolerance? Wrong regulation?

Total IgM for screening for congenital infections?

Total IgM in 2/7 Children elevated



CMV Diagnostics - Serology

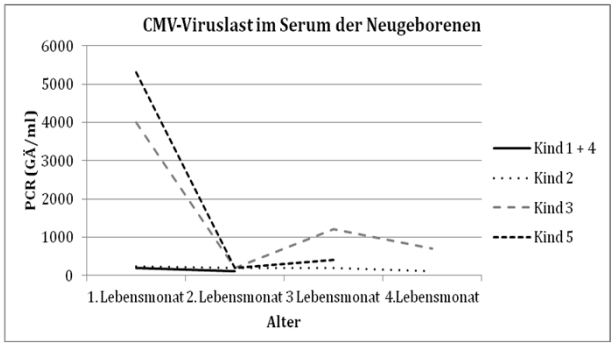
7 children with congential CMV infection

CMV IgM
- positive at birth: 2
- positive with delay: 1
- Never positive: 4

CMV IgG
- strongly positive: 6
- weakly positive: 1

Congenital CMV infection diagnostics

- **CMV serum viral loads**

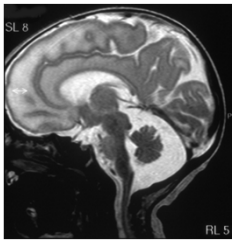


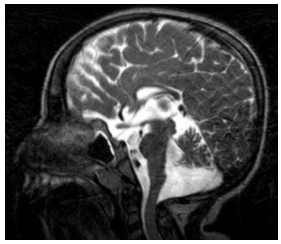
Congenital CNS infections – diagnose

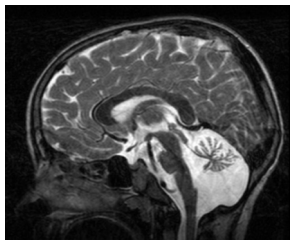
- Toxoplasmosis: before birth: Serial spec. IgG/igM, Avidity; PCR Amnion fluid.
  After birth: comparison child / maternal antibodies, PCR
- syphilis: infection per se: spec. IgM antibodies (FTA- ABS, TPPA, TPHA)
  activity: cardiolipin antibodies: RPR, VDRL (comparison with maternal findings)
  PCR from different compartments
- Parvovirus: Serology, PCR
- VZV: clinical findings; maternal history; spec. IgM
- Rubella: spec. IgM; PCR
- CMV: PCR Urine, blood within 3 weeks after birth
- HSV: PCR CSF and blood;

- PCR testing in multiple compartments

Basic principles III
Age at infection and lesion pattern

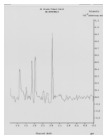




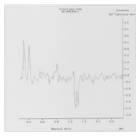


CMV

non-ketotic hperglycinemia



mitochondrial disease



Different noxious agents causing similar damage during vulnerable phases of intrauterine development

Basic principles IV
Pathomechanisms of infection-related brain damage

- Direct (Neuronal cell destruction)
- Bacterial toxins
- Immune evasion
- Secondary vascular disease
- Specific immune reaction
- Overwhelming inflammation
- True autoimmunity
- Systemic failure (cardiovascular, respiratory)
- Single nucleotid polymorphisms (predisposition, clinical course)
- ..
- ..
- ..
- ..

Immune evasion

- Secretion von Immunotoxins
- Secretion of cytokine or receptor analoga
- Hidance from the immune system (viral latency, encapsulated bacteria), antigen hypervariability (influenza)
- Killing of immune cells (HIV)
- Inhibition of the adaptive immune response (MHC blockage)
- Inhibition of complement
- Inhibition of cytokines, chemokines
- Modulation of apoptosis
- Interference with TLR
- Blockage of intrinsic celular pathways

Group B streptococcus

- Beta haemolysin / cytolysin
  - Pore forming cytolysin
  - Pro-apoptotic
  - Pro-inflammatory

VZV – CNS

Respiratory inoculation
1. **Replication upper respiratory tract**

2. **Viremia + fever**

3. **Systemic replication in liver and lymph nodes**

4. **Viremia (cell-bound, T-cells)**

← Native immune respons
NK-cells
IFN-alpha

VZV inhibits
MHC-I-Expression (CD8+ response)
MHC-II-Expression (CD4+ response)

→ Skin disease

← CD4+ TH1- response (IFN-gamma)
CD8+cytotox. response

Clinical manifestations

Neonatal
Congenital
Perinatal

Infection as leading symptom

Infection as cofactor in systemic disease

Congenital CNS infections – TORCH

T oxoplasmosis
O thers
R ubella
C ytomegatlovirus
H erpes simplex ???

syphilis
Varicella zoster virus
Listeriosis
HIV
Zika virus
Parvovirus

Congenital CNS infections

Common findings in congenital infections

Microcephaly, calcifications, subependymal cysts, lentikulostriatal vasculopathy, parenchymatous lesions, chorioretinitis, hydrocephalus, malformations

Specific changes

Toxoplasmosis:	**infection of all organs**: Myocardits, Hepatitis
syphilis:	**infection of all organs**. Granulomatous CNS infection, meningitis, uveitis, cerebral vasculopathy (tooth malformations, sceletal dysplasia)
Parvovirus:	**infection of erythropoiesis precursors**: Hydrops
VZV:	**Infection of neurons, ectodermal structurs, vessels**..: skin lesions, sceletal hypoplasia, stroke
HIV:	**T-cells**, microglial activation, opportunistic infections
Rubella:	**multiple organs, endothelial cells**: cardiac malformation
CMV:	**all CNS cells, persistence in myeloic cells. Epithelial cells**. Hepatitis, Sepsis….
HSV:	**neuronal cells, ectodermal cells**,

Congenital CNS infections

More frequent:
Congenital: dystrophy, symptoms of septicemia
Older age: White matter lesions, cerebral calcifcation, retinal scars, deafness

Toxoplasmosis 18 months

CMV deafness

Congenital CNS infections – time at infection

- Toxoplasmosis: Risk of transmission (Tachyzoites) increases with gestational age
  Risk of disease decreases with gestational age
- Syphilis: from early pregnancy or during birth

- Parvovirus: maximum risk in 2nd trimenon infection
- VZV: congenital varicella: infection until 20 (28) weeks of gestation
  neonatal varicella: infection during last 4 weeks of pregnancy
  most severe neonatal varicella: infection between -5 to +2 days

- Rubella: highest risk (80%) after infection within the first 12 weeks of gestation
- CMV: intrauterine, mother seronegative (30% risk of transmission)
  intrauterine, **mother seropositive (low risk)**
  neonatal,
- HSV: intrauterine: rare. Especially with maternal primary infection during 1st trimenon.
  Perinatal: more frequent. 35% encephalitis

Congenital infection treatment

Problems

- Chronic (intracellular)
- Limited access of antimicrobial agents to the CNS
- Gastrointestinal uptake of antimicrobail agents

Congenital infections - treatment

	Treatment effective?
• Toxoplasmosis: pyrimethamine, sulfadiazine. > 12 months?, different treatment regimen, steroids in ocular involvement.	Uncertain
• Parvovirus B 19: no causal therapy	
• VZV: aciclovir for 7 days, or longer? Or higher doses? Immunglobulins after perinatal exposition and preterms after exposition	No good data
• Rubella: no causal treatment	
• CMV: ganciclovir for 6weeks, or longer? Valganciclovir (! Granulocytopenia)	Benefit for hearing
• HSV: aciclovir high dose for 3 weeks, or longer?	Good data Clear benefit
• syphilis: penicillin G for 2 weeks	

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CMV congenital - therapy

- **CMV = Herpesvirus (latency and persistence)**
- **Suppression not elimination**

Ganciclovir (Valganciclovir)

J Pediatr. 2003 Jul;143(1):16-25.

Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial.

Kimberlin DW[1], Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Kiell JM, Soong SJ, Whitley RJ; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group.

Hearing with 6 months better

J Clin Virol. 2009 Dec;46 Suppl 4:S22-6. doi: 10.1016/j.jcv.2009.08.012. Epub 2009 Sep 18.

Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system.

Oliver SE[1], Cloud GA, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Soong SJ, Whitley RJ, Kimberlin DW; National Institute of Allergy, Infectious Diseases Collaborative Antiviral Study Group.

Cognition better at 6 and 12 months

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CMV congenital delayed therapy

Clin Pediatr (Phila). 2014 May;53(5):444-8. doi: 10.1177/0009922813510204. Epub 2013 Nov 25.

Treatment of late-onset hearing loss in infants with congenital cytomegalovirus infection.

Amir J[1], Attias J, Pardo J.

⊕ Author information

Abstract

OBJECTIVE: To evaluate the effect of antiviral treatment on late-onset hearing loss in infants with congenital cytomegalovirus infection.

DESIGN: The database of all infants who had normal hearing at birth, and treated for late-onset hearing loss was collected. The primary study endpoint was the need for a cochlear implant at the last follow-up visit.

RESULTS: Twenty-one infants met the inclusion criteria. Brain stem-evoked response audiometry testing revealed hearing loss in 35 of 42 ears (83%). Mean age at diagnosis of hearing loss was 7.4 ± 3.7 months and onset of antiviral therapy 10.3 ± 7.8 months. None of the ears showed further deterioration as referred to pretreatment values. Hearing thresholds improved in 29 ears (69%). None of the patients needed a cochlear implant.

CONCLUSIONS: In children with late-onset hearing loss due to cytomegalovirus infection, antiviral treatment appears to prevent further deterioration and produce improvement. Controlled studies are needed to verify this observation.

Later start of treatment also effective?

Differential diagnoses

- Genetical disorders
- Metabolic disorders

Microcephaly- intracranial calcifications

OMIM	Name	Gen	Mikrozephalie	Verkalkung
#251290	Pseudo-TORCH-S.	OCLN	konnatal	Band-like, PV, BG, Thalamus, Pons, Kleinhirn
#225750	Aicardi-Goutières-S.	AGS1: TREX1 AGS2: RNASEH2B AGS3: RNASEH2C AGS4: RNASEH2A AGS5: SAMHD1	Progressiv	BG und PV
#613730	"Hemorrhagic destruction of the brain, subependymal calcification and cataracts"	JAM3	Postnatal	Subependymal
#261600	Phenylketonurie	PAH	Progressiv	Progressiv
#614219	Adams-Oliver-S.	DOCK6	+	PV
#259775	Raine-S.	FAM20C	+	+
%236795	"3-Hydroxyisobutyric-aciduria"	Autosomal rezessiv	+	+
#216400	Cockayne-S. Typ A	ERCC8	+	BG
#192430	Velocardiofaziales S.	TBX1	+	BG
#164200	Oculodentodigitales S.	Connexin 43-Gen	+	BG
#613990	Konnatale Dyskeratose	TINF2	+	+
#261630	Hyperphenylalaninämie, BH4-abhängig	QDPR	+	+
185300	Sturge-Weber-S.	Unbekannt	Selten	Kortikal
#530000	Kearns-Sayre-S.	Verschiedene mitochondriale Gene	+	BG
#606777 #612126	Glut-1 Defekt	SLC2A1	Progressiv	PV (selten)
*611492	Carboanhydrase II-Defizienz	CA2	+	+
#214150	Cerebro-Okulo-Fazio-Skelettales S.	ERCC6	+	PV, BG
#160900	Myotone Dystrophie	DMPK	+	BG

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Perinatal / Neonatal CNS infections –

Neonatal Meningitis

- Group B Streptococcal infections
- E coli
- Listeriosis

- Enterobacter, Citrobacter, Serratia, Pseudomonas, Neisseria, mycoplasma

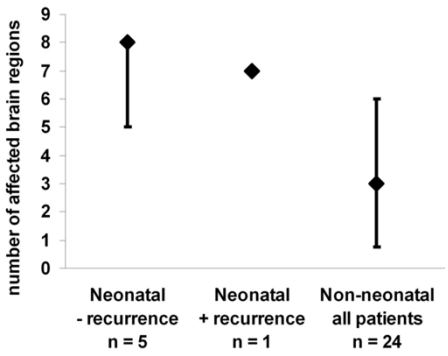
Neonatal Encephalitis

- VZV
- HSV

- Parechovirus
- Enterovirus
- LCM

Neonatal HSV infection

HSV Neuroimaging
Number of brain regions involved



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HSVE diagnosis

- Clinical symptoms not specific
- Febrile neonate
  rate of HSVE = rate of bacterial meningitis

- PCR
- MRI: Diffusion-weighted imaging most sensitive at early stages

28

HSVE therapy

- Aciclovir 3 x 20 mg/kg for 3 weeks
- Longer??

Format: Abstract ▾ Send to ▾

N Engl J Med. 2011 Oct 6;365(14):1284-92. doi: 10.1056/NEJMoa1003509.

Oral acyclovir suppression and neurodevelopment after neonatal herpes.

Kimberlin DW[1], **Whitley** RJ, Wan W, Powell DA, Storch G, Ahmed A, Palmer A, Sánchez PJ, Jacobs RF, Bradley JS, Robinson JL, Shelton M, Dennehy PH, Leach C, Rathore M, Abughali N, Wright P, Frenkel LM, Brady RC, Van Dyke R, Weiner LB, Guzman-Cottrill J, McCarthy CA, Griffin J, Jester P, Parker M, Lakeman FD, Kuo H, Lee CH, Cloud GA; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group.

⊕ Author information

the infants were randomly assigned to immediate acyclovir suppression (300 mg per square meter of body-surface area per dose orally, three times daily for 6 months) or placebo. Cutaneous recurrences were treated with open-label episodic therapy.

RESULTS: A total of 74 neonates were enrolled--45 with CNS involvement and 29 with skin, eye, and mouth disease. The Mental Development Index of the Bayley Scales of Infant Development (in which scores range from 50 to 150, with a mean of 100 and with higher scores indicating better neurodevelopmental outcomes) was assessed in 28 of the 45 infants with CNS involvement (62%) at 12 months of age. After adjustment for covariates, infants with CNS involvement who had been randomly assigned to acyclovir suppression had significantly higher mean Bayley mental-development scores at 12 months than did infants randomly assigned to placebo (88.24 vs. 68.12, P=0.046). Overall, there was a trend toward more neutropenia in the acyclovir group than in the placebo group (P=0.09).

Complications

- Cognitive
- Motor
- Epilepsy

- NMDAR encephalitis?

Neonatal meningitis

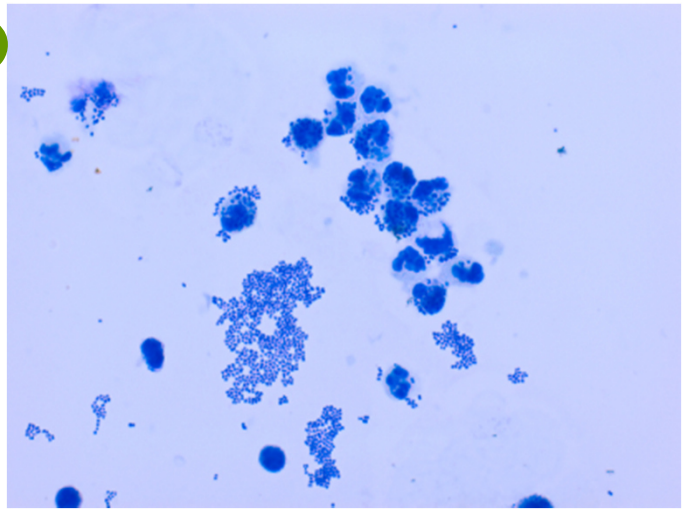
Neonatal Meningitis

Neonatal Meningitis
- Early onset: within 7 days
- Late onset: 8-18 days

Neonatal Septicemia
- Early onset: within 72 hours
- Late onset: after 72 hours

Literature: eminence >>>> evidence

?



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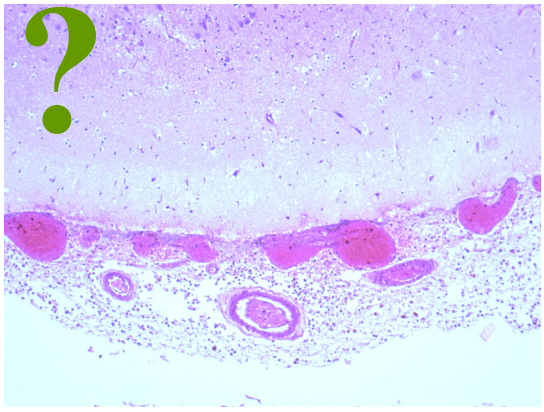

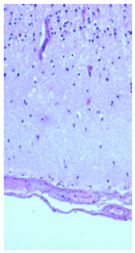

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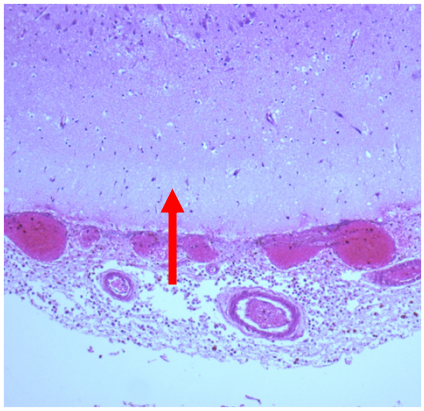

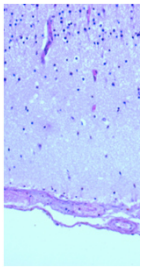

Neurotoxins

Bacterial meningitis = meningoencephalitis

- Systemic infection
- Meningeal infection
- Arterial vasculopathy
- Venous infarction
- „Toxic“ CNS effects (oxidative stress, cytokines)
- Elevated intracranial pressure

Neonatal bacterial meningitis diagnose

- Risk factors (maternal GBS colonization, maternal peripartal antibiotic treatment?, maternal infection, rupture of membranes > 18 h; amniotic fluid abnormal, preterm neonates)
- Clinical symptoms not specific
  (systemic infection, seizures, arterial hypotension, hypo / hyperthermia, apnea, dyspnea hyperexcitability, prolonged capillary refill > 2sec….)
- Blood CRP; IL6 and clinical controls
- Lumbar puncture in all late-onset septicemias (> 3 days of life)
- Gram stain + CSF / blood culture including antibiogram
- CSF IL6?
- Panbacterial / panmycotic PCR

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Bacterial meninigitis treatment

- antibiotic treatment
- Better to stop early than to start late?
- CRP > 10 mg/l, IL6 > 50 ng/l, leuko- or granulocytopenia

- Early onset: Ampicillin + tobramycin (+ cefotaxim in severe cases)
- Late onset: cefotaxim + tobramycin (no pre-treatment)
  Ceftazidim + vancomycin (+ pre-treatment, preterm, assumed gram- septicemia
- + necrotizing enterocolitis or no response: meropeneme + vancomycin

- Adopt to microbial agent, so far identified (antibiogram)
- Assumed candida infection: fluconazole

- **Know Your Own Spectrum of Infections and drug resistance**

Aachen

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Vergleich **gramnegativer** Erreger 2015 2014 2013– Uniklinik RWTH Aachen – **Station KI08**
(Anteil der **resistenten oder intermediär empfindlichen** Erreger in Prozent)

Antibiotika / Erreger - Gruppen	*Acinetobacter baumannii-kompl.*			*Citrobacter spp.*			*Enterobacter spp.*			*Escherichia coli*			*Klebsiella spp.*			*Pseudomonas aeruginosa*			*Serratia spp.*			*Stenotrophomonas maltophilia*		
Jahr	***2015***	*14*	*13*	**2015**	14	13	***2015***	*14*	*13*	***2015***	*14*	*13*	***2015***	*14*	*13*	***2015***	*14*	*13*	***2015***	*14*	*13*	***2015***	*14*	*13*
Anzahl Isolate	***3***	*0*	*1*	**17**	*2*	*8*	***30***	*15*	*24*	***59***	*13*	*31*	***87***	*15*	*34*	***8***	*8*	*4*	***6***	*2*	*6*	***3***	*7*	*2*
Ampicillin				**94%**	100%	100%	**97%**	87%	100%	**56%**	46%	47%	**100%**	100%	100%				**100%**	100%	100%			
Amp/Sulbactam				**71%**	100%	50%	**93%**	87%	96%	**49%**	38%	29%	**22%**	27%	9%				**33%**	100%	83%			
Piperacillin				**71%**	100%	100%	**47%**	13%	67%	**56%**	38%	42%	**87%**	100%	100%	**25%**	13%	50%	**17%**	0%	17%			
Pip./Tazobactam				**24%**	50%	38%	**37%**	21%	54%	**8%**	8%	16%	**12%**	13%	6%	**25%**	13%	50%	**17%**	0%	0%			
Cefuroxim				**92%**	100%	100%	**95%**	87%	96%	**29%**	23%	13%	**14%**	33%	9%				**100%**	100%	100%			
Cefotaxim				**35%**	50%	38%	**38%**	20%	67%	**20%**	15%	10%	**8%**	27%	3%				**17%**	0%	0%			
Ceftazidim				**24%**	50%	50%	**37%**	20%	67%	**20%**	23%	10%	**8%**	27%	3%	**0%**	13%	25%	**17%**	0%	0%			
Ciprofloxacin / Levofloxacin	**0%**	0%	0%	**0%**	0%	38%	**10%**	0%	25%	**12%**	31%	10%	**3%**	7%	3%	**13%**	25%	0%	**0%**	0%	0%			
Moxifloxacin				**0%**	0%	29%	**18%**	0%	22%	**21%**	50%	4%	**5%**	20%	3%				**0%**	50%	0%			
Imipenem	**0%**	0%	0%	**0%**	0%	0%	**0%**	0%	0%	**0%**	0%	0%	**1%**	0%	0%	**13%**	29%	25%	**0%**	0%	0%			
Meropenem	**0%**	0%	0%	**0%**	0%	0%	**0%**	0%	0%	**0%**	0%	0%	**1%**	0%	0%	**13%**	38%	25%	**0%**	0%	0%			
Gentamicin	**0%**	0%	0%	**0%**	0%	13%	**7%**	0%	29%	**3%**	8%	6%	**2%**	7%	6%	**25%**	25%	50%	**0%**	0%	0%			
Trimethoprim/ Sulfamethoxazol	**0%**	0%	0%	**0%**	0%	0%	**7%**	0%	25%	**34%**	38%	23%	**7%**	27%	3%				**0%**	0%	0%	**0%**	0%	0%

Duration of treatment

- 3 weeks or longer
- Neuroimaging
- Re-lumbar puncture

Bacterial meningitis supportive therapy

- Intensive care treatment
- Normal blood pressure
- Normal blood glucose electrolytes
- Steroids ?

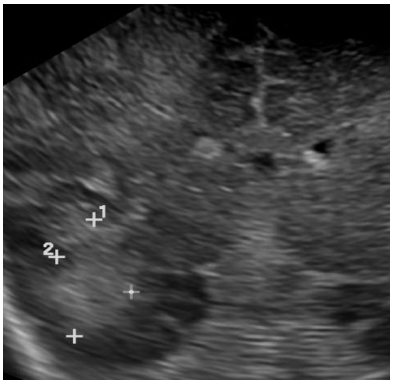
Bacterial meningitis - complications

- Neurological complications
  - infarction, abscess
- Complications of septicemia
  - lung: respiratory failure
  - cardiovascular failure; arterial hypotension, PDA; PFC
  - renal: failure
  - liver: failure
  - gastrointestinal: NEC

?

Example – preterm neonate

11. Day of life



- Preterm newborn, 31 completed weeks of gestation
- Day 8.:
- late onset septicemia Citrobacter
- intravenous therapy

- Complication

Brain abscess

(Cerebral) infection – infection as cofactor

Periventricular leukomalacia

Infection promoting oxidative stress

Oligodendroglia of preterm neonates is exceptionally susceptible to oxidative stress

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Thank you very much